JACC Vol. 13, No. 7
June 1989:1503–5

Editorial Comment

Ischemia—Silent or Manifest: Does It Matter?*

KANU CHATTERJEE, MB, FRCP, FACC

San Francisco, California

Clinical expressions of myocardial ischemia are protean and include angina and symptoms related to ventricular systolic and diastolic dysfunction and arrhythmia. The consequences of ischemia are also variable and range from no immediate adverse effects to sudden death, myocardial infarction and severe impairment of cardiac performance and heart failure. However, myocardial ischemia can occur without any clinical manifestations and can be clinically totally silent. There is a multitude of evidence for the existence of "silent" myocardial ischemia (1).

Reversible left ventricular regional wall motion abnormalities, either stress-induced or spontaneous, in the absence of angina, provide evidence for silent myocardial ischemia. Global and regional myocardial lactate production, a metabolic marker of ischemia, has been documented in the absence of angina. Reversible myocardial thallium perfusion defects at rest or during dipyridamole or exercise stress occur rather frequently without associated angina. On the basis of wall motion abnormalities, metabolic dysfunction, reversible scintigraphic perfusion defects and ischemic changes on the stress electrocardiogram (ECG), the incidence rate of silent myocardial ischemia has been estimated to be approximately 34% in patients with coronary artery disease (2).

However, recently popularized ambulatory electrocardiography in studies to detect ischemia have revealed a much higher incidence of silent ischemia (3). It has been documented that ST segment shifts, both depression and elevation, on the ambulatory ECG correlate well with other markers of myocardial ischemia (4). Electrocardiographic monitoring has revealed that in patients with stable exertional angina resulting from obstructive coronary artery disease, approximately 70% of episodes of ischemia are asymptomatic. In postinfarction patients and in patients with mixed angina, a similar, higher incidence of asymptomatic ST segment shifts has been reported (5,6).

Present study. In this issue of the Journal, Langer et al. (7) report the frequency, anatomic correlates and significance of symptomatic and asymptomatic ST segment shifts in patients with unstable angina. Of 135 patients reported, 89 (66%) had ST shifts on Holter monitor and the majority (68%) of these 89 patients had only silent ischemia. In only 6% of patients were ST shifts always symptomatic, and in the remaining 26% of patients both symptomatic and asymptomatic ST shifts occurred. As reported in other studies (2–6), this study also indicates that silent ischemia typically occurs in patients with established coronary artery disease, and the majority of the episodes of ischemia are not accompanied by angina. Indeed, in this study, 92% of the episodes of ST shift were asymptomatic and only 8% were symptomatic.

Mechanisms of silent ischemia. Although it appears to be established that silent myocardial ischemia is frequent in patient with coronary artery disease, its pathophysiologic mechanisms and significance are beginning to be clarified. Myocardial ischemia results from the imbalance between myocardial oxygen requirements and oxygen supply. An increase in the determinants of myocardial oxygen demand may precipitate myocardial ischemia if the oxygen requirements outstrip the capacity to increase coronary blood flow. In patients with exertional angina with predictable and relatively fixed exercise threshold, increased oxygen requirement is believed to be the principal mechanism for angina during exercise. The mechanism for asymptomatic ischemia (e.g., ST shift or reversible thallium perfusion defects during exercise tests) in these patients is also likely to be similar.

During pacing-induced myocardial ischemia, symptomatic or asymptomatic, there is an inadequate increase in coronary blood flow to balance the increase in heart rate–blood pressure product (8). However, in patients with chronic stable angina, asymptomatic episodes of ischemia detected during Holter ECG monitoring may occur without any significant change in heart rate; similarly, symptomatic ST shifts during Holter monitoring also occur with little or no change in heart rate (4). Selwyn et al. (9) observed that an increase in heart rate of >10 beats/min preceding the onset of the ST shift in the ambulatory ECG occurred only during 20% of episodes of ischemia. Transient myocardial perfusion defects detected by positron emission tomography with or without angina also occurred in many instances without any significant increase in heart rate (4,9). These findings suggest that a primary reduction in coronary blood flow rather than an increase in oxygen requirements is the principal mechanism for these ischemic episodes, and the mechanism is

*Editorials published in *Journal of the American College of Cardiology* reflect the views of the authors and do not necessarily represent the views of JACC or the American College of Cardiology.

From the Division of Cardiology, University of California, San Francisco, San Francisco, California.

Address for reprints: Kanu Chatterjee, University of California, San Francisco, Division of Cardiology, 505 Parnassus, 1186-Moffitt, San Francisco, California 94143.

0735-1097/89/$3.50

JACC Vol. 13, No. 7
June 1989:1503–5

similar whether ischemia is manifest or silent. In patients with variant angina, reduction of coronary blood flow resulting from segmental spasm of the epicardial coronary arteries appears to induce both symptomatic and asymptomatic spontaneous ischemia (10).

Mechanisms of silent ischemia in unstable angina. In the present study reported by Langer et al. (7), the incidence of multivessel coronary artery disease and left main coronary artery stenosis was much higher in patients with asymptomatic ST shifts on Holter monitoring. Although it is not clear from this study whether both symptomatic and asymptomatic ST shifts were associated with a similar incidence of multivessel disease, previous studies (11) have reported a high incidence of multivessel and left main coronary artery disease in patients with unstable angina. Thus, both manifest and silent myocardial ischemia in patients with unstable angina are associated with similar anatomic correlates—i.e., presence of multivessel coronary artery disease. The mechanisms for spontaneous ischemia in patients with "unstable angina," whether manifest or silent, also appear to be similar. In this study by Langer et al. (7), there was a slight but significant increase in rate-pressure product 10 min before onset of both symptomatic and asymptomatic ST shifts. These findings suggest that increased myocardial oxygen requirements might have been contributory in precipitating ischemia. It needs to be emphasized, however, that the magnitude of increase in rate-pressure product preceding ischemia was relatively small.

Furthermore, a fair proportion of the episodes of ST shifts occurred without any prior change or even decrease in rate-pressure product. Thus, a primary reduction or an inadequate increase in coronary blood flow must be considered as a potential mechanism for myocardial ischemia in these patients. The proposed mechanisms for spontaneous reduction in coronary blood flow in patients with unstable angina include mechanical obstruction of the atherosclerotic epicardial coronary arteries by labile thrombus or platelet aggregates and dynamic reversible increase in arterial tone mediated by vasoactive substances (12). Whatever the mechanisms might be, they are likely to be similar for both symptomatic and asymptomatic ischemia.

Prognosis of silent ischemia. Is the prognosis of patients with silent ischemia any different from that of patients with manifest ischemia? That recurrence of angina after acute myocardial infarction (postinfarction angina) is associated with unfavorable prognosis has been well documented (13). "Silent ischemia" in patients after infarction is also associated with a poorer prognosis (14). An unfavorable 1 and 6 month prognosis in the presence of silent ST segment shifts in patients with unstable angina has been reported previously (15,16). The report of Langer et al. (7) also suggests that in patients with both symptomatic and asymptomatic unstable angina, ST shifts are associated with an in-hospital unfavorable outcome. Although these investigators noted that "more patients with recurrent chest pain associated with any ST shift during Holter monitoring had an unfavorable outcome than did patients with an ST shift alone," the difference was at best modest. Thus, it appears that at least in certain subsets of patients with established coronary artery disease, anatomic pathology, pathophysiology and prognosis of both silent and manifest myocardial ischemia are very similar.

Treatment. Should therapeutic approach be different for manifest and silent ischemia? Ideally, therapy should be based on the knowledge of the pathophysiologic mechanisms of ischemia in individual patients, which, however, are variable in different ischemic syndromes and are not always apparent. Fortunately, available therapy appears to be equally effective for the control of both manifest and silent myocardial ischemia. Antianginal drugs, including nitrates, calcium entry blocking agents and beta-adrenergic blocking drugs, decrease both symptomatic and asymptomatic episodes of ischemia. Similarly, myocardial perfusion therapy by angioplasty or coronary artery bypass surgery decreases the frequency of both symptomatic and asymptomatic ischemia. Thus, from available data, it appears that the same therapy is effective for the control of both symptomatic and asymptomatic myocardial ischemia. However, as asymptomatic ischemia in patients with established coronary artery disease appears to be associated with similar consequences and prognosis as with symptomatic ischemia, the time has arrived, I believe, to direct therapeutic objectives for the detection and treatment of "ischemia" whether or not it manifests clinically or remains silent.

References

1. Chatterjee K. Role of nitrates in silent myocardial ischemia. Am J Cardiol 1987;60:18H–25H.
2. Cohn PF. Silent myocardial ischemia in patients with a defective anginal warning system (editorial). Am J Cardiol 1980;45:697–702.
3. Deanfield JE, Maseri A, Selwyn AP, et al. Myocardial ischemia during daily life in patients with stable angina: its relation to symptoms and heart rate changes. Lancet 1983;2:753–8.
4. Deanfield JE, Shea M, Ribiero P, et al. Transient ST-segment depression as a marker of myocardial ischemia during daily life. Am J Cardiol 1984; 54:1195–200.
5. Cohn PF, Sodums MT, Lawson WE, Vlay SC, Brown EJ Jr. Frequent episodes of silent myocardial ischemia after apparently uncomplicated myocardial infarction. J Am Coll Cardiol 1986;8:982–5.
6. Chierchia S, Glazier JJ, Gerosa S. A single-blind, placebo-controlled study of effects of atenolol on transient ischemia in "mixed" angina. Am J Cardiol 1987;60:36A–40A.
7. Langer A, Freeman MR, Armstrong PW. ST segment shift in unstable angina: pathophysiology and association with coronary anatomy and hospital outcome. J Am Coll Cardiol 1989;13:1495–502.
8. Chatterjee K, Rouleau J-L, Parmley WW. Medical management of patients with angina: has first-line therapy management changed? JAMA 1984;252:1170–6.
9. Selwyn AP, Shea M, Deanfield JE, Wilson R, Horlock P, O'Brila A.

Character of transient ischemia in angina pectoris. Am J Cardiol 1986;58: 21B–5B.

10. Maseri A, Severi S, DeNes M, et al. "Variant angina": one aspect of a continuous spectrum of vasospastic myocardial ischemia. Am J Cardiol 1978;42:1019–25.
11. Codeca L, Brundage B, Chatterjee K. Unstable rest angina: coronary anatomy and evaluation of medical therapy. J Ital Cardiol 1981;11:1905–13.
12. Fuster V, Steele PM, Chesebro JH. Role of platelets and thrombosis in coronary atherosclerotic disease. J Am Coll Cardiol 1985;5:175B–84B.
13. Schuster EH, Bulkley BH. Early post infarction angina: ischemia at a distance and ischemia in the infarct zone. N Engl J Med 1981;305:1101–5.
14. Theroux P, Waters DD, Halphen C, et al. Prognostic value of exercise testing soon after myocardial infarction. N Engl J Med 1979;301:341–5.
15. Gottlieb SO, Weisfeldt ML, Ouyang P, Mellitus ED, Gerstenblith G. Silent ischemia as a marker for early unfavorable outcomes in patients with unstable angina. N Engl J Med 1986;314:1214–9.
16. Nademanee K, Intarachot V, Josephson MA, Rieders D, Mody FV, Singh BN. Prognostic significance of silent myocardial ischemia in patients with unstable angina. J Am Coll Cardiol 1987;10:1–9.